REMARKS

Reconsideration of this application is requested. Claims 1-36 are in the case.

I. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

Claims 1-25 have been provisionally rejected on obviousness-type double patenting grounds over claims appearing in five copending applications listed in the penultimate paragraph on page 2 of the action. It is respectfully requested that this rejection be placed in abeyance until it is known which of the alleged conflicting claims are allowed.

II. THE OBVIOUSNESS REJECTION

Claims 1-15, 18-19 and 22-25 have been rejected under 35 USC 103 as being unpatentable over Martin et al or Sommadossi et al when taken in view of Von Borstel et al (WO 89/03837) and Falcone et al. The rejection is traversed for the following reasons.

The invention of the present application is directed to a method for the prevention or treatment of toxicity due to a pyrimidine nucleoside analog. The method comprises the steps of administering to an animal a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

As correctly noted by the Examiner, neither Martin nor Sommadossi teaches the use of acylated uridine or cytidine derivatives. In an attempt to cure this deficiency, the Examiner relies on Von Borstel '837 and asserts that it would have been obvious to a person of ordinary skill to have substituted acylated uridine or

cytidine as described by Von Borstel in place of the free uridine disclosed by Martin and Sommadossi in order to increase serum and tissue levels of uridine and thereby reduce toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of the nucleoside analog. Applicants disagree for the following reasons.

Martin (and others, e.g. Peters et al (Brit. J. Cancer 57:259-265, 1988)) disclose the use of uridine to reduce toxicity of 5-fluorouracil. This permits 5-FU dose escalation and a consequent net improvement in antitumor efficacy.

However, unexpected results have been obtained according to the present invention when acyl derivatives of uridine of the invention, e.g. 2', 3', 5'-triacetyluridine (TAU), are administered orally in conjunction with 5-FU. Neither Martin nor Peters were able to induce even partial (50%) regressions of the murine adenocarcinoma colon 26 with high-dose 5-FU alone at the maximum tolerated dose (100 mg/kg/week). In contrast, high-dose 5-FU in combination with oral TAU consistently results in a high incidence (60-80%) of complete regressions of established tumors.

Moreover, Kralovansky et al (Cancer Chemother Pharmacol 1993; 32:243-8), report that uridine administration after 5FU does not reduce the severity of gastrointestinal activity due to 5FU, although it does accelerate recovery from GI damage. In contrast, in human clinical trials with oral TAU administered after high dose 5FU, there is a remarkable reduction of gastrointestinal damage indicated by the no grade 3 or grade 4 mucositis or diarrhea in patients receiving up to 100 mg/m^2 5FU per week (Kelsen et al, Journal of Clinical Oncology, in press). Such toxicities are not uncommon in patients receiving normal clinical doses (500 to 600 mg/m^2 per week) of 5FU.

Thus, acyl derivatives of pyrimidine nucleosides provide unexpected benefits beyond those that have been reported for parenteral or oral administration of uridine when used to modify the toxicity and efficacy of antineoplastic pyrimidine nucleoside analogs. These same unexpected benefits are observed when TAU is administered with an inhibitor or uridine phosphorylase, e.g. benzolyoxybenzylacyclouridine, but not when the uridine phosphorylase inhibitor alone is administered (M. el Kouni, unpublished results).

Given the deficiencies of Martin and Sommadossi, the Examiner resorts to the Von Borstel disclosure. This reference describes methods of delivering acyl derivatives of uridine or cytidine for the treatment of cardiac insufficiency, myocardial infarction, cirrhosis of the liver, cerebrovascular disorders, respiratory distress syndromes and diabetes. The specifically claimed methodology is in no way disclosed or suggested by Von Borstel, either when taken alone or in combination with Martin and/or Sommadossi. A person of ordinary skill would not therefore have been motivated to combine the references as suggested by the Examiner. Absent any such motivation to combine, it is clear that a *prima facie* case of obviousness is not generated by these references.

As conceded in the paragraph bridging pages 4-5 of the action, neither Martin, Sommadossi nor Von Borstel teaches the use of an inhibitor of uridine nucleoside phosphorylase. The Examiner relies on Falcone as a disclosure relating to the use of an inhibitor of uridine nucleoside phosphorylase, namely benzylacyclouridine.

In response, Martin, Sommadossi and Von Borstel do not give rise to a *prima facie* case of obviousness of the methodology as claimed in claim 1 for the above-discussed reasons. Claims 18-19 are also clearly patentably distinguished over that combination of references irrespective of the Falcone disclosure. Withdrawal of the

outstanding obviousness rejection based on Martin, Sommadossi, Von Borstel and/or Falcone is believed to be in order, and this is requested.

Claims 16-17 and 20-20 have been rejected under 35 USC 103 as being unpatentable over Bhalla et al when taken in view of Von Borstel (WO 89/03838) and U.S. patent 4,017,606 to Hanze. That rejection is traversed for the following reasons.

Bhalla fails to describe the use of acylated deoxycytidines in place of free deoxycytidine. In order to cure this deficiency, the Examiner relies on Von Borstel '838 in view of mention in that disclosure of acylated deoxycytidine. In response, a person of ordinary skill would not have been motivated to arrive at the presently claimed method on the basis of the combined disclosures of Bhalla and Von Borstel. There is no suggestion in Bhalla when taken alone or in combination with Von Borstel of the methodology as claimed in this case.

Hanze is likewise deficient from the standpoint of giving rise to a *prima facie* case of obviousness against the presently claimed method. Hanze discloses pyrimidine nucleosides and nucleotides useful for inhibiting deaminating enzymes. There would have been no reason for a person of ordinary skill to rely on this disclosure in the context of the presently claimed method.

Withdrawal of the outstanding obviousness rejections is now believed to be in order. Such action is respectfully requested.

III. THE 35 USC 112, FIRST PARAGRAPH, REJECTION

The specification has been objected to, and claims 1, 3-15, 18-19, and 24-25 rejected, under 35 USC 112, first paragraph, for the reasons that the specification is

enabling only for claims limited to specific nucleosides listed on page 6 of the action. In response, the invention is not limited to those specific compounds recited by the Examiner. To amend the claims to recite those derviatives would be an undue limitation to the claims, and would enable third party infringers to take advantage of the invention while readily avoiding infringement. Withdrawal of this rejection is accordingly respectfully requested.

The specification and claim 11 have been objected to because of the word "tegafur". In response, claim 11 and specification have been amended to present the word as "Tegafur". According to the Merck Index (copy of entry number 9060 attached), it appears that Tegafur is a trade name, not a trademark.

Objection has been made to the claims on the ground that the position of the fluorine in fluorouridine is not indicated. The claims have been amended to rectify this informality.

Allowance of the application is awaited.

Respectfully submitted,

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